Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Chayakrit Krittanawong MD , Bharat Narasimhan MD , Zhen Wang PhD , Hafeez Ul Hassan Virk MD , Ann M. Farrell MLIS , HongJu Zhang PhD , W.H. Wilson Tang MD

PII: S0002-9343(20)30549-0
DOI: https://doi.org/10.1016/j.amjmed.2020.05.046
Reference: AJM 15832

To appear in: *The American Journal of Medicine*

Please cite this article as: Chayakrit Krittanawong MD , Bharat Narasimhan MD , Zhen Wang PhD , Hafeez Ul Hassan Virk MD , Ann M. Farrell MLIS , HongJu Zhang PhD , W.H. Wilson Tang MD , Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis, *The American Journal of Medicine* (2020), doi: https://doi.org/10.1016/j.amjmed.2020.05.046

Title: Association Between Egg Consumption and Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Running Title: Egg Consumption and Risk of Cardiovascular Outcomes

Author list: Chayakrit Krittanawong, MD[1,2,3], Bharat Narasimhan, MD[3], Zhen Wang, PhD[4,5], Hafeez Ul Hassan Virk, MD[6], Ann M. Farrell, MLIS[8], HongJu Zhang, PhD[8], W.H. Wilson Tang, MD[9]

Author Affiliations:

[1]The Michael E. DeBakey VA Medical Center, Houston, TX,

[2]Section of Cardiology, Baylor College of Medicine, Houston, TX,

[3]The Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, New York, NY,

[4]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN,

[5]Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[6]Department of Cardiovascular Diseases, Einstein Medical Center, Philadelphia, PA,

[8]Mayo Clinic Libraries, Mayo Clinic, Rochester, MN,

[9]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio, USA

Word Count: 1,460

Funding source(s) related to this manuscript: None

Conflict of interest statement for all authors: None

Author Contributions: All authors had access to the data, contributed significantly to the work and a role in writing the manuscript

Corresponding Author:

Chayakrit Krittanawong, MD

Baylor College of Medicine

Section of Cardiology

1 Baylor Plaza, Houston, TX 77030

Tel: 713-798-4951

Email: Chayakrit.Krittanawong@bcm.edu

Keywords: Egg consumption; Cardiovascular disease; Stroke; Acute myocardial infarction;

Systematic review; Meta-analysis

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association

ABSTRACT

Introduction: Considerable controversy remains on the relationship between egg consumption and cardiovascular disease risk. The objective of this systematic review and meta-analysis was to explore the association between egg consumption and overall cardiovascular disease events.

Methods: We systematically searched Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception from 1966 through January 2020 for observational studies that reported the association between egg consumption and cardiovascular disease events. Two investigators independently reviewed data. Conflicts were resolved through consensus. Random-effects meta-analyses were used. Sources of heterogeneity were analyzed.

Results: We identified 23 prospective studies with a median follow-up of 12.28 years. A total of 1,415,839 individuals with a total of 123,660 cases and 157,324 cardiovascular disease events were included. Compared to the consumption of no or 1 egg/day, higher egg consumption (more than 1 egg/day) was not associated with significantly increased risk of overall cardiovascular disease events (pooled hazard ratios, 0.99; 95% CI, 0.93-1.06; p<0.001; I^2= 72.1%). Higher egg consumption (more than 1 egg/day) was associated with a significantly decreased risk of coronary artery disease (pooled hazard ratios, 0.89; 95% CI, 0.86-0.93; p<0.001; I^2= 0%), compared to consumption of no or 1 egg/day.

Conclusions: Our analysis suggests that higher consumption of eggs (more than 1 egg/day) was not associated with increased risk of cardiovascular disease, but associated with a significant reduction in risk of coronary artery disease.

Clinical Significance

- Consumption of more than one egg per day was not associated with an increased risk of cardiovascular disease.
- Consumption of more than one egg per day was associated with a reduction in the risk of coronary artery disease.
- Consumption of more than one egg per day was not associated with an increased risk of stroke.

INTRODUCTION

Eggs are a nutrient-dense (e.g., minerals, folate, B vitamins, and fat-soluble vitamins), a rich source of bioactive compounds (e.g., lutein and zeaxanthin) and high-quality protein.(1) Nutrients and bioactive compounds in eggs may theoretically contribute to improving cardiovascular disease.(2) However, eggs are also high in cholesterol, and, for example, one large egg contains approximately 186 mg of cholesterol. Although no direct evidence that egg consumption can lead to elevated cholesterol levels, the American Heart Association (AHA) Dietary Guidelines Revision 2000 has recommended the public to consume less than 300 mg/day of cholesterol to minimize the elevation of blood cholesterol.(3) Interestingly, the more recent Dietary Guidelines for Americans 2015–2020, has no longer provide limits on egg intake but recommended egg intake as healthy eating patterns.(4) Previous studies have been demonstrated inconsistent results of associations of egg consumption with cardiovascular disease, leading to considerable controversy.(5-8) To date, previous studies on egg consumption and cardiovascular disease risk have been inconclusive. The objective of this systematic review and meta-analysis

was to explore the association between egg consumption and cardiovascular disease.

METHODS

Search strategy

We developed search strategies for Ovid MEDLINE, Ovid Embase, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science from database inception to January 2020. The search strategies were peer-reviewed by experienced librarians. The language or date of publication was not limited. The strategies included MeSH and Embase terms as well as keywords including egg, egg consumption, cardiovascular disease, cardiovascular events, coronary artery disease, acute myocardial infarct, acute coronary syndrome, stroke, or heart failure. (online supplementary)

Study selection

Studies were included in this analysis if the following criteria: the study design was either prospective or cross-sectional, the exposure of interest was egg consumption, the outcome was combined cardiovascular disease events, coronary artery disease, acute myocardial infarct, acute coronary syndrome, stroke or heart failure, and the investigators reported hazard ratios with 95% confidence intervals. Reviews, editorials, non-human studies, letters without sufficient data, studies of other exposures and diseases were excluded.

Data extraction

Two reviewers (CK and BN) performed data extraction using a standard extraction form and then review by other reviewers (HH and HZ). Authors, year of publication, study name, study

location, years of follow-up, sample size (number of participants and incident cases), participants' characteristics (age and sex), endpoints (e.g., coronary artery disease , stroke), outcomes ascertainment, egg consumption categories, covariates adjusted in the multivariable analysis, hazard ratios (95% confidence intervals) for all categories of egg consumption were extracted from included studies. Conflicts were resolved through consensus.

Quality assessment

Two independent reviewers performed the quality assessment (BN and HJ) using the Newcastle-Ottawa quality assessment scale, a validated scale for non-randomized studies in meta-analyses. Conflicts were resolved through consensus. We assigned scores of 0-3, 3.5-6, and 6.5-9 for a low, moderate, and high quality of studies, respectively. We consulted dietitians and nutritionists for servings, nutritional units. We contacted the authors if the data of interest were not directly shown in the publications.

Statistical analysis

In this meta-analysis, the hazard ratios (HRs) and 95% confidence intervals were considered as the effect size for all studies. Any results stratified by sex were separated as two cohorts. We used the DerSimonian & Laird random-effects method to pool HRs from the included studies. We also conducted subgroup analyses based on sex, study location, number of cases and participants, duration of follow-up, egg consumption measurements, study quality, and whether diet variables or cholesterol levels were controlled for in models. The difference between subgroups was evaluated using the interaction test proposed by Altman.(9) Heterogeneity between studies was measured by I^2. Substantial heterogeneity was defined as I^2 >50%. Stata

version 11 (Stata Corp) and R version 3.6.1 were used for statistical analyses. A two-sided p-value of less than 0.05 was considered as statistically significant.

RESULTS

Figure 1 shows the results of literature research and selection. We identified 530 articles from PubMed, SCOPUS, and COCHRANE database from 1966 to January 31, 2020. We identified 23 prospective studies with a median follow-up of 12.28 years. A total of 1,415,839 individuals with a total of 123,660 cases and 157,324 cardiovascular disease events were included. We categorized cardiovascular disease as 94,175 coronary heart disease, 3,112 heart failure, 19,173 acute myocardial infarction, and 40,864 stroke cases. The study population included 565,385 individuals from China, 495,972 from the United States, 10,802 from New Zealand, 166,790 from Japan, 6636 from Finland, 488 from Australia, 14,185 from Spain, 702 from Lithuania, 65,364 from France, 26,930 from Sweden, 9248 from Korea, 1781 from the UK, 7216 from Mediterranean countries, 14337 from the Middle East, 6282 from Africa and 23,721 from South America. We did not find a significant association between egg consumption and increased risk of overall cardiovascular disease events (HR, 0.99; 95% CI, 0.93-1.06; I^2= 72.1%). (Figure 2) Compared to the consumption of no or 1 egg/day, higher egg consumption (more than 1 egg/day) was associated with a significantly decreased risk of coronary artery disease (HR, 0.89; 95% CI, 0.86-0.93; I^2= 0%). (Figure 3); however, higher egg consumption (more than 1 egg/day) was not associated with the risk of stroke (HR, 0.92; 95% CI, 0.84-1.02; I^2= 60.1%). (Figure 4) In subgroup analyses using study type (prospective vs. retrospective), geography, and follow up year, we did not find any associations between egg consumption and risk of cardiovascular disease. There was no significant difference between the subgroups. After excluding studies with

a moderate risk of bias, we did not find any associations between egg consumption and risk of cardiovascular disease.

DISCUSSION

The present meta-analysis, including studies from 1966 to 2020, identified no significant association between egg consumption and risk of cardiovascular disease events, but we found that egg consumption (> 1 egg per day) is associated with a reduction in coronary artery disease risk. Similarly, the previous meta-analysis of 8 observational studies showed no significant association between egg intake and cardiovascular disease events.(10) However, there is substantial heterogeneity in that meta-analysis due to adjusted variables in included studies. A recent meta-analysis found moderate egg consumption (≤ 1 egg per day) is not associated with cardiovascular disease risk overall.(11) These results are consistent with a subgroup analysis of our study. From evidence to date, either 1 egg or more than 1 egg consumption is not associated with cardiovascular disease. Another meta-analysis of overall dietary cholesterol, including eggs, found no significant either coronary artery disease or stroke risks.(12) However, those included studies in that meta-analysis were heterogeneous and lacked the methodologic rigor to draw any conclusions. To date, studies of egg consumption and coronary artery disease, including meta-analyses, have been inconsistent. The latest meta-analysis of intake of 12 major food groups, including eggs, suggested an optimal eggs consumption may lower risk of coronary artery disease .(13) Previous meta-analysis included 7 prospective studies found no significant association with coronary artery disease by comparing high versus low egg consumption (RR 0.97, 95% CI 0.88 to 1.07).(14) However, the results may be confounded by the inclusion of diabetic patients who have higher cardiovascular disease risks due to dietary patterns than non-

diabetic patients.(15) Another meta-analysis of 9 prospective studies reported that egg consumption was not associated with an increased risk of coronary artery disease but was associated with a significantly elevated risk of coronary artery disease in diabetic populations.(10) Interestingly, our study found no association between egg consumption and coronary artery disease in both diabetes groups and non-diabetes groups.

Egg consumption may reduce coronary artery disease via a mechanism of promoted carotenoid absorption(16,17), enhanced HDL cholesterol function(18,19), increased bioactive compounds (e.g., lutein and zeaxanthin), resulting in protecting against atherosclerosis.(20) The discrepancy of previous studies may be due to small sample sizes, a lack of adjustment for overall dietary pattern, ethnic difference, and only adjusting for blood glucose instead of excluding diabetic patients. For example, a recent meta-analysis found that egg consumption up to one egg per day is probably associated with a slightly lower cardiovascular disease risk among Asians.(21) Most importantly, Individuals who consume egg may consume processed meats or bacon or high salt intake.

There are certain limitations to our meta-analysis. First, participants may have changed their dietary pattern during the long follow-up period, particularly in the US (e.g., the change in recommendation from the Dietary Guidelines for Americans 2015–2020). Second, self-reported diet data could potentially lead to measurement errors. Third, the statistical power was limited in subgroup analyses of subtypes of stroke (ischemic vs. hemorrhagic) or heart failure (heart failure with preserved ejection fraction vs. heart failure with reduced ejection fraction). Forth, dietary data collection with food frequency questionnaires inevitably leads to some measurement errors. Finally, the study findings are observational and cannot establish causality.

In conclusion, our analysis suggests that higher consumption of eggs (more than 1 egg/day) was not associated with increased risk of cardiovascular disease, but a reduction in risk of coronary artery disease.

CRediT author statement

Krittanawong: Conceptualization, Methodology, Software, Data extraction, Writing- Original draft preparation; **Narasimhan:** Data curation, Data extraction, Writing- Original draft preparation; **Virk:** Data extraction, Data curation, Reviewing and Editing; **Wang**: Statistical analyses and validation; **Farrell:** Data extraction; **Zhang:** Data extraction, Data curation; **Tang:** Supervision, Reviewing and Editing

REFERENCES

1. Andersen CJ. Bioactive Egg Components and Inflammation. Nutrients 2015;7:7889-913.
2. Djousse L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. The American journal of clinical nutrition 2008;87:964-9.
3. Krauss RM, Eckel RH, Howard B et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000;102:2284-99.
4. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary. Guidelines for Americans. https://health.gov/our-work/food-nutrition/2015-2020-dietary-guidelines/guidelines/ Last accessed on May 12, 2020
5. Qin C, Lv J, Guo Y et al. Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. Heart 2018;104:1756.
6. Jang J, Shin M-J, Kim OY, Park K. Longitudinal association between egg consumption and the risk of cardiovascular disease: interaction with type 2 diabetes mellitus. Nutrition & Diabetes 2018;8:20.
7. Xu L, Lam TH, Jiang CQ et al. Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. European Journal of Nutrition 2019;58:785-796.
8. Guo J, Hobbs DA, Cockcroft JR et al. Association between egg consumption and cardiovascular disease events, diabetes and all-cause mortality. European Journal of Nutrition 2018;57:2943-2952.
9. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ (Clinical research ed) 2003;326:219.
10. Rong Y, Chen L, Zhu T et al. Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies. BMJ (Clinical research ed) 2013;346:e8539.
11. Drouin-Chartier J-P, Chen S, Li Y et al. Egg consumption and risk of cardiovascular disease: three large prospective US cohort studies, systematic review, and updated meta-analysis. BMJ (Clinical research ed) 2020;368:m513.
12. Berger S, Raman G. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. 2015;102:276-94.
13. Bechthold A, Boeing H, Schwedhelm C et al. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Critical reviews in food science and nutrition 2019;59:1071-1090.
14. Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of Egg Consumption and Risk of Coronary Heart Disease and Stroke. Journal of the American College of Nutrition 2016;35:704-716.
15. Tran NL, Barraj LM, Heilman JM, Scrafford CG. Egg consumption and cardiovascular disease among diabetic individuals: a systematic review of the literature. Diabetes Metab Syndr Obes 2014;7:121-137.
16. Chung H-Y, Rasmussen HM, Johnson EJ. Lutein Bioavailability Is Higher from Lutein-Enriched Eggs than from Supplements and Spinach in Men. The Journal of Nutrition 2004;134:1887-1893.

17. Kim JE, Gordon SL, Ferruzzi MG, Campbell WW. Effects of egg consumption on carotenoid absorption from co-consumed, raw vegetables. The American journal of clinical nutrition 2015;102:75-83.
18. Blesso CN. Egg phospholipids and cardiovascular health. Nutrients 2015;7:2731-47.
19. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. Jama 2007;298:786-98.
20. Ciccone MM, Cortese F, Gesualdo M et al. Dietary intake of carotenoids and their antioxidant and anti-inflammatory effects in cardiovascular care. Mediators Inflamm 2013;2013:782137-782137.
21. Drouin-Chartier J-P, Chen S, Li Y et al. Egg consumption and risk of cardiovascular disease: three large prospective US cohort studies, systematic review, and updated meta-analysis. BMJ (Clinical research ed) 2020;368:m513-m513.

FIGURE LEGENDS

Figure 1: Study design. This flow chart illustrates the selection process for published reports

Figure 2: Hazard ratio of cardiovascular diseases associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

Figure 3: Hazard ratio of coronary artery disease associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

Figure 4: Hazard ratio of stroke associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

Figure 1: Study design. This flow chart illustrates the selection process for published reports

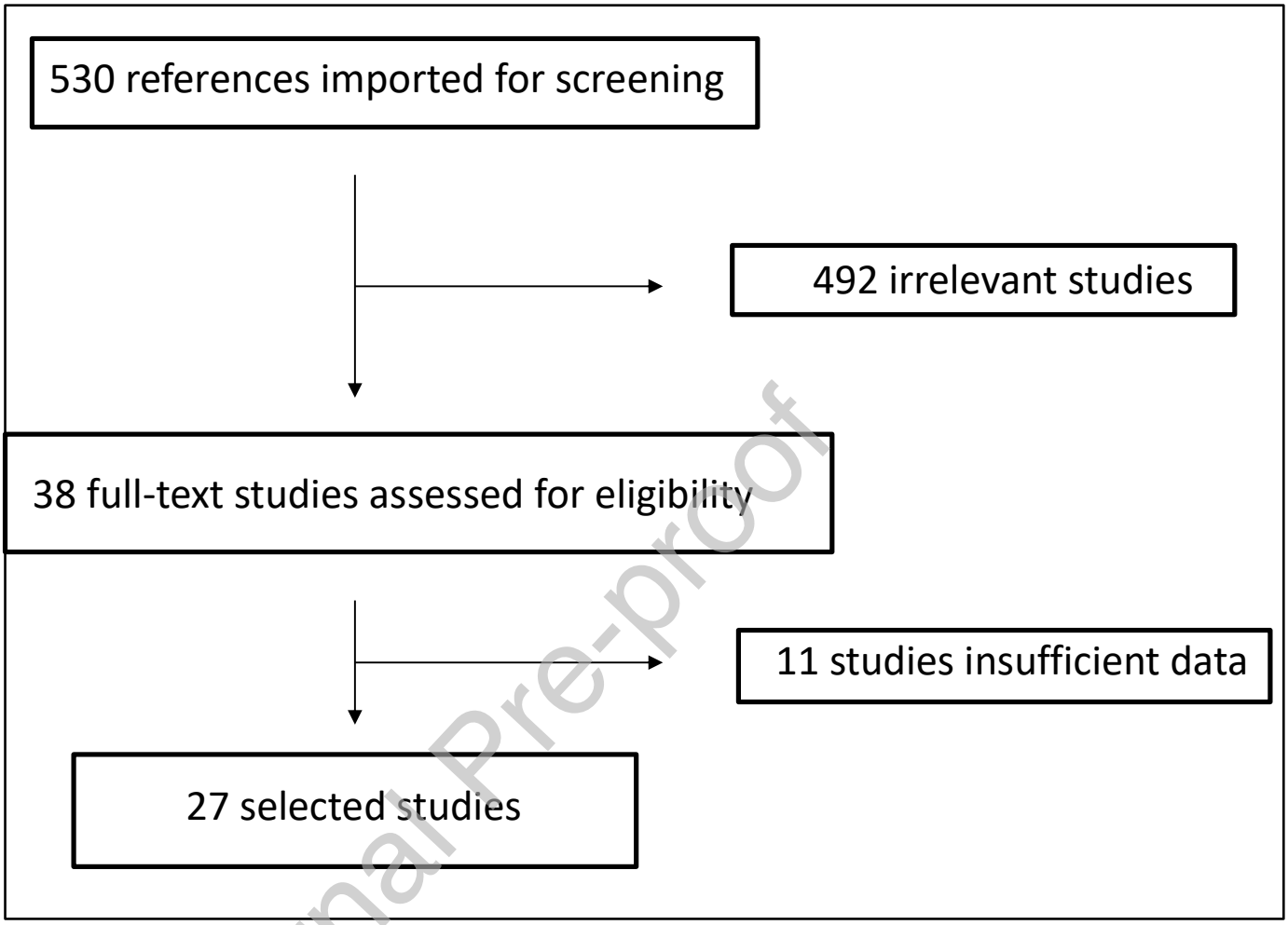

Figure 2: Hazard ratio of cardiovascular diseases associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

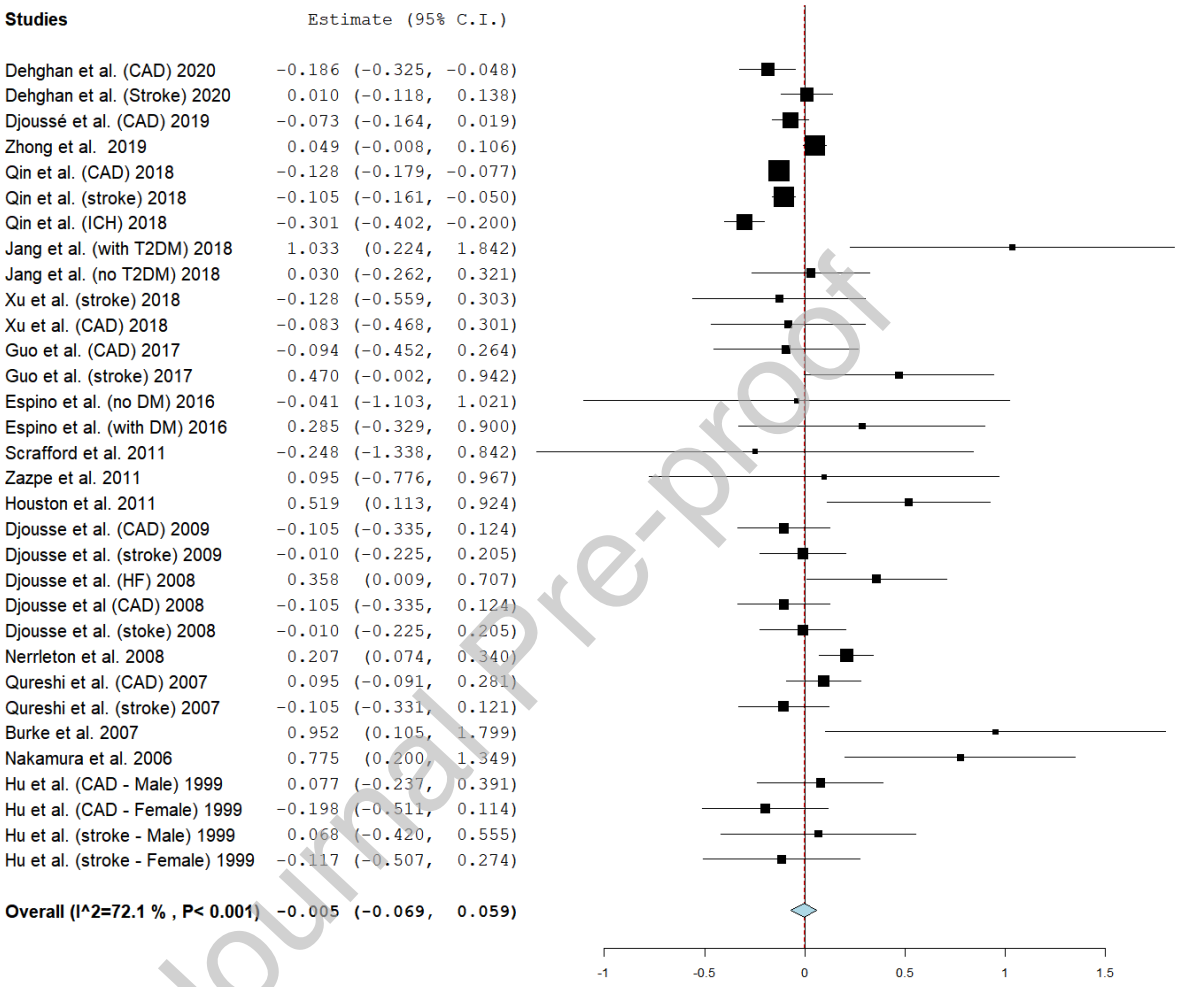

Figure 3: Hazard ratio of coronary artery disease associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

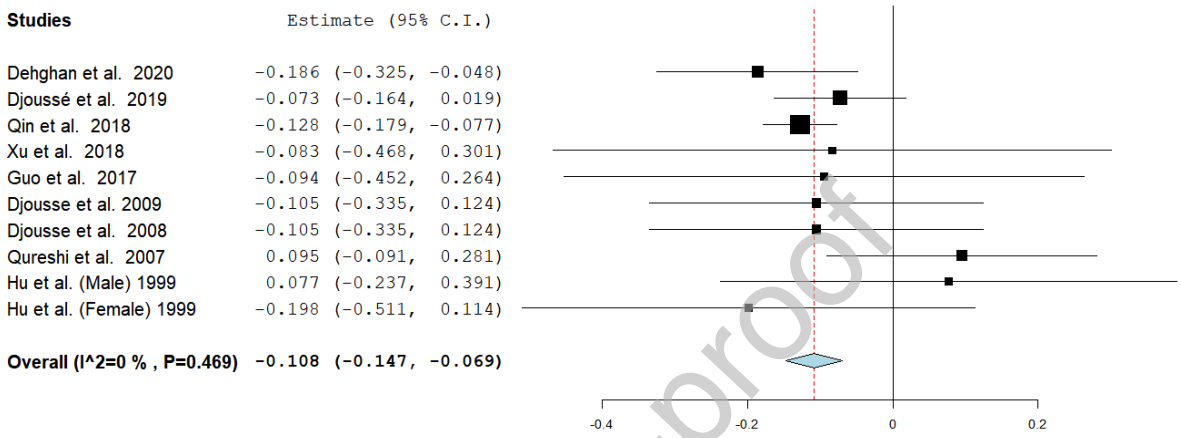

Figure 4: Hazard ratio of stroke associated with egg consumption (more than 1 egg/day vs. no/1 egg/day)

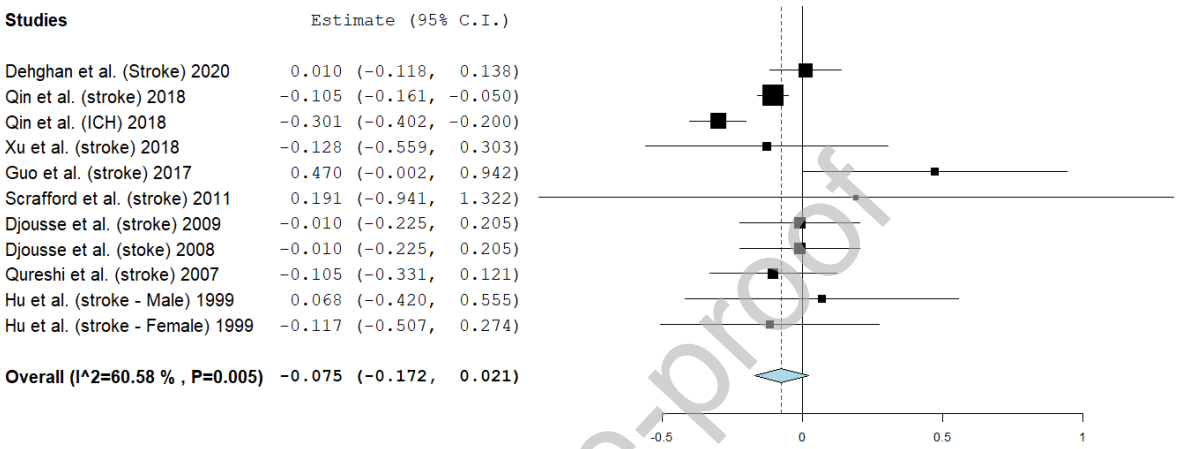

Table 1. Characteristics of Included Studies

Study	Year	Country	Study design	Men %	Mean age	Follow-up term y	No. of subjects	No. of cases	Outcome assessments	Outcome	Exposure assessments	Adjusted variables
Deghan	2020	21	Cohort	41.9	50.6 ± 9.9	4.6	146,011	3410	Self-reported questionnaire	cardiovascular disease, All cause mortality, major cardiovascular disease, Lipid profile, blood pressure	FFQ	Age, sex, education, urban or rural location, smoking, physical activity, history of diabetes, fruit and vegetables, red meat, poultry, fish, dairy, percentage of energy from carbohydrates, and total energy intake.
Djoussé	2019	USA	Cohort	90.1	64.4	3.24	188,267	10,260	ICD codes	MI	FFQ	age, sex, race, education, body mass index, smoking, exercise, alcohol intake, DM
Zhong	2019	United States	Cohort	44.9	51.6	17.5	29615	5400	Questionnaire	cardiovascular disease	FFQ	Age, sex, race/ethnicity, education, total energy, smoking status, smoking pack-years , BMI, , alcohol consumption, and use of hormone therapy
Xu	2018	China	Cohort	28	62.1	9.8	280224	26855	Medical records	cardiovascular disease , Fasting sugar, BP, Lipid panel, BMI, All cause mortality	FFQ	Age, Sex, Socioeconomic position (education, income and occupation)
Qin	2018	China	Cohort	41	50.7	8.9	461213	83977	ICD Codes	cardiovascular disease , IHD, Stroke, MCE	Diet Questionnarie	age at recruitment and sex, education level , household income, marital status, alcohol consumption, tobacco smoking, physical activity in MET-hours/day, BMI , waist to hip ratio, prevalent hypertension, use of aspirin, family history of cardiovascular disease , intake of multivitamin supplementation and dietary pattern
Jang	201	Korea	Cohor	47.	52	7.3	924	570	Biennial questionnaire	cardiovascular disease , T2DM	SQFFQ	Age, sex, educational level, residential area, monthly household income, alcohol drinking, smoking in pack-years, and physical activity level. dietary supplement use, history of hypertension and

	8		t	8			8					dyslipidemia, and the intake levels of total energy, total vegetables, total fruits, red meat, fiber, and vitamin E. body mass index
Guo	2017	UK	Cohort	100	61.6	22.8	17811	18863	Self-reported questionnaire	cardiovascular disease , T2D, All cause mortality	FFQ	Age, BMI, energy and alcohol intake, smoking, social class, energy expenditure, FH of MI or T2DM. Sugar, fruit, red meat and fibre intake
Espino	2016	Mediterranean countries	Cohort	49.3	66.5	5.8	72162	342	Medical records	MI, stroke & death (CV causes)	FFQ	Age, Sex, BMI, DM,HTN,HLD, FH of premature coronary artery disease
Scrafford et al. (M) [33]	2011	USA	Cohort	100	42.1	8.8	68331	261	ICD codes I20-I25; I60-69	CHD mortality; stroke mortality;	Semi quantitative FFQ	Age, energy, marital status, race/ethnicity, smoking, BMI, WHR, DM, hypertension, dietary variables
Scrafford et al. (F)	2011	USA	Cohort	0	42	8.9	81133	142	ICD codes I20-I25; I60-69	CHD mortality, stroke mortality;	Semi quantitative FFQ	Age, energy, marital status, race/ethnicity, smoking, BMI, WHR, DM, hypertension, dietary variables
Zazpe et al	2011	Spain	Cohort	40.9	38.4	6.1	14,185	91	Medical record	cardiovascular disease	Semi quantitative FFQ	Age, sex, energy, alcohol, smoking, BMI, DM, hypertension, physical activity, adherence to Mediterranean food pattern; hyperlipidemia, family history of cardiovascular disease
Houston et al.	2011	USA	Cohort	45.5	74.5	9	19411	203	Medical record	cardiovascular disease	Interviewer administered questionnaire	Age, sex, race, energy, education, field center, smoking, alcohol, physical activity, BMI, multivitamin, aspirin, or statin, oral estrogen use, DM, hypertension, fiber, protein, or saturated fat intake
Djousse et al. (M)	2010	USA	Cohort	42.8	73.2	11.3	16682	142	Medical record	DM	Picture-sort FFQ	Age, race, field center, BMI, physical activity, energy, smoking, alcohol, fiber intake
Djousse et a	201	USA	Cohor	57.	72.	11.3	223	161	Medical record	DM	Picture-sort FFQ	Age, race, field center, BMI, physical activity, energy, smoking, alcohol, fiber intake

l. (F)	0		t	2	1		0					
Djousse et al. (M)	2009	USA	Cohort	100	53.5	20	20,703	1921	Self-report or medical record	DM	Semi quantitative FFQ	age, BMI, smoking, alcohol consumption, exercise, red meat intake, quintiles of energy intake, fruits and vegetables, saturated fatty acids, trans fatty acids, polyunsaturated fatty acids, family history of diabetes, and history of hypercholesterolemia and hypertension.
Djousse et al. (F)	2009	USA	Cohort	0	54.5	11.7	36,295	2112	Self-report or medical record	DM	Semi quantitative FFQ	age, BMI, smoking, alcohol consumption, exercise, red meat intake, quintiles of energy intake, fruits and vegetables, saturated fatty acids, trans fatty acids, polyunsaturated fatty acids, family history of diabetes, and history of hypercholesterolemia and hypertension.
Djousse et al	2008	USA	Cohort	100	53.7	20.4	21,275	1084	Medical record	HF	Semi quantitative FFQ	Age, BMI, smoking, alcohol consumption; DM, AF, hypertension, physical activity; history of valvular disease and treatment of cholesterol
Djousse et al.	2008	USA	Cohort	100	53.7	20.4	21,327	8071	The Endpoint Committee of the PHS	All-cause mortality; MI; stroke;	Semi quantitative FFQ	Age, BMI, smoking, alcohol consumption; DM, AF, hypertension, physical activity, history of valvular disease and treatment of cholesterol
Nettleton et al.	2008	USA	Cohort	45.5	54.2	13.3	14,153	1140	ICD-9 (codes 428 and I50, ICD-10	HF	Interviewer administered questionnaire	Age, race, education, BMI, physical activity, energy, smoking, alcohol, fiber, sodium, meat, fruit consumption, baseline history of disease
Qureshi et al.	2007	USA	Cohort	38.7	49.2	20	97342	1239	ICD codes 9	IHD; stroke; all-cause mortality;	Diet questionnaire	Age, sex, serum cholesterol, hypertension, waist girth
Burke et al	2007	Australia	Cross-sectional	50.8	NA	14	488	130	Medical records, ICD codes 9, 10, 410-414, 427, 428	CHD	Interviewer administered questionnaire	Age, sex, race, DM, serum cholesterol, smoking, hypertension, BMI, educational status
Nakamura et	2006	Japan	Prospective	47.8		11	90,735	462	Medical record	CHD	Semi quantitative FFQ	Age, sex, BMI, hypertension, diabetes, use of cholesterol-lowering drugs, smoking (never, ex-, and current smoker), alcohol drinking (six categories), whether or not intended to avoid cholesterol-rich diets, consumption frequencies of

al												meat, fish, vegetables, fruits, and cohort effects.
Monto nen	2005	Finland	Cohort	53	53.7	23	4304	383	Medical records	DM	FFQ	age, sex, body mass index, smoking, family history of diabetes, geographic area
Hu et al. (M)	1999	USA	Cohort	100	53.3	8	37,851	866	Medical record	CHD, stroke,	Diet questionnaire	Age, sex, smoking, BMI, parental history of MI, multivitamin supplement, hypertension, physical activity, menopausal statas
Hu et al. (F)	1999	USA	Cohort	0	45.9	14	80,082	939	Medical record	CHD, stroke,	Diet questionnaire	Age, sex, smoking, BMI, parental history of MI, multivitamin supplement, hypertension, physical activity, menopausal statas
Mann et al.	1997	New Zealand	Cohort	38	33.4	13.3	10,802	525	ICD codes 410-414	All-cause mortality; IHD	Semi quantitative FFQ	Age, sex, smoking, social class